UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: December 15, 2016

SUBJECT: Thiamethoxam. Human Health Risk Assessment for Tolerances on Imported Bananas.

PC Code: 060109
Decision No: 508490
Petition: 5E8401

Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D429508
Registration No: N/A
Regulatory Action: Tolerance without a US registration
Case No.: 7614
CAS No.: 153719-23-4
40 CFR: §180.565

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1.0 Executive Summary

Thiamethoxam is a broad spectrum nitroguanidine insecticide which belongs to the pesticidal class of compounds known as the neonicotinoids (Group 4A; Insecticide Resistance Action Committee). It has activity against sucking and chewing insects on a wide variety of crops. Thiamethoxam appears to interfere with the nicotinic acetylcholine receptors of the insect's nervous system, but the specific receptor site is unknown at this time. It does not inhibit cholinesterase or interfere with sodium channels and, therefore, has a different mode of action than organophosphate, carbamate, and pyrethroid insecticides.

Thiamethoxam is currently registered for use on a variety of agricultural food crops (foliar and seed treatment), in livestock and poultry houses, on turf grass, sod farms, golf courses, ornamental plants grown in greenhouses, Christmas trees, and residential lawns. It is also registered for use in or on domestic dwellings, food handling establishments, and commercial, institutional, and industrial areas.

This risk assessment addresses the proposed establishment of a permanent tolerance (without US registration) for residues of thiamethoxam in/on imported bananas. Tolerances for residues of thiamethoxam are listed in 40 CFR §180.565 and are expressed in terms of the combined residues of the insecticide thiamethoxam and its metabolite CGA-322704. Metabolite CGA-322704 is also the registered active ingredient clothianidin (tolerance listings in 40 CFR 180.586). Clothianidin (hereinafter referred to as CGA-322704) has a complete toxicological database and appears to have effects in mammals that are different from those of thiamethoxam. A separate risk assessment that addresses risks from CGA-322704 residues resulting from the direct application of CGA-322704 (clothianidin), as well as risks from residues of CGA-322704 coming from thiamethoxam uses has been conducted (D436256, J. Cowins, November 10, 2016), and there are no risk estimates of concern as a result of the proposed import tolerance for thiamethoxam residues.

Hazard

The toxicological database for thiamethoxam is complete and acceptable for selecting toxicity endpoints and points of departure (PODs) for risk assessment. The scientific quality of the available toxicology studies is relatively high and the toxicity profile of thiamethoxam can be characterized for most effects, including potential carcinogenicity, mutagenicity, developmental toxicity, neurotoxicity, and immunotoxicity. An inhalation toxicity study is not available for thiamethoxam; however, the Hazard and Science Policy Council (HASPOC) recommended, based on a weight-of-evidence (WOE) approach, that the study is not required (TXR# 0052354).

In mammals, toxicological effects are seen primarily in the liver, kidney, testes, and blood cellular system. In addition, developmental neurological effects were observed in rats. These developmental effects are being used to assess risks associated with acute exposures to thiamethoxam, and the liver and testicular effects are the basis for assessing longer-term exposures.

There is no indication of quantitative or qualitative susceptibility in the developmental toxicity studies. There is evidence of quantitative susceptibility in the developmental neurotoxicity study

and both two-generation reproductive studies. However, clear no observed adverse effects levels (NOAELs) were identified for the susceptibility in the 2-generation reproduction and developmental neurotoxicity (DNT) studies and the endpoints and doses chosen for risk assessment are protective of the susceptibility observed in these studies. Therefore, the Health Effects Division (HED) has reduced the Food Quality Protection Act (FQPA) Safety Factor (SF) to account for sensitivity of infants and children from 10X to 1X. Therefore, the level of concern (LOC) is based on an uncertainty factor (UF) of 100X (10X for extrapolation from animal to human, 10X for potential variation in sensitivity among members of the human population and 1X for the FQPA SF).

Thiamethoxam is classified as "not likely to be carcinogenic to humans."

In acute lethality studies, technical thiamethoxam is slightly toxic to rats and moderately toxic to mice via the oral route of exposure (Toxicity Category III); it is of low toxicity to rats via the dermal (Toxicity Category III) and inhalation routes (Toxicity Category IV). It is not irritating to the skin and minimally irritating to the eye, and is not a dermal sensitizer.

No new toxicity data have been received for thiamethoxam since the previous risk assessment (D425511, D. McNeilly et al., 7/2/2015). All endpoints remain the same as the previous risk assessment, except for incidental oral and inhalation exposure. HED updated the point of departure for the incidental oral assessment (from the 90 day dog study to the 28 day dog study) and chose an inhalation endpoint specific for children <6 years old to refine the risk assessment for exposure to children. The choice of endpoints specific for children <6 years old for incidental oral, dermal and inhalation exposure were done as refinements because short-term exposure estimates exceeded the level of concern when using the conservative endpoint of testicular effects, which are not relevant for sexually immature children. While a chronic dietary endpoint specific for children <6 years old could have also been chosen, this was not necessary from a risk assessment perspective as the use of the current testicular effects is conservative and protective, and does not result in any risk estimates of concern.

Residue Chemistry
HED has examined the residue chemistry database for thiamethoxam. Pending submission of a revised Section F, there are no residue chemistry issues that would preclude establishing a 0.03-ppm tolerance for the combined residues of thiamethoxam and CGA-322704 in imported bananas.

Exposure
There are no residual uncertainties with respect to dietary, residential, or occupational exposure.

HED has assessed dietary (food + drinking water) exposures to thiamethoxam. The acute and chronic dietary exposure and risk estimates are all well below HED's LOC for all population subgroups and durations of exposure, and are not of concern.

There are no new residential uses associated with this action; however, there are existing residential uses that were previously assessed and reflect updates to HED's 2012 Residential

SOPs[1] along with a revision to the inhalation POD for children < 6 years of age (D359207, M. Collantes, July 24, 2009; and D406746, M. Crowley, Dec 4, 2012). No residential exposure scenarios (handler and post-application) resulted in risk estimates of concern.

Exposures related to turf activities have been combined with chronic dietary exposure estimates (as an estimate of background dietary exposure from food and water) to assess the worst-case short-term aggregate exposure. The short-term aggregate MOEs range from 500 to 580. These risk estimates are greater than the LOC of 100 and are not of concern.

An occupational exposure risk assessment is not required for establishing import tolerances.

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment. Given the use patterns for thiamethoxam as well as the health-protective assumptions throughout this risk assessment, it is unlikely that any geographic, ethnic, or socioeconomic population will have increased exposure relative to the standard population subgroups assessed by Office of Pesticide Programs (OPP).

Human Studies Review
This risk assessment is based, in part, on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Residential Standard Operating Procedures (SOPs) are (1) subject to ethics review pursuant to 40 CFR Part 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the agency website.

2.0 HED Recommendations

HED has no objection to the establishment of a 0.03-ppm tolerance for thiamethoxam in/on imported bananas (i.e., tolerance without US registration). The specific tolerance recommendations are discussed in 2.2.

2.1 Data Deficiencies

None.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate method, high-performance liquid chromatography (HPLC) Method AG-675, is available to enforce the recommended tolerance. The FDA multi-residue methods in *PAM*

[1] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

Volume I are not adequate for tolerance enforcement, as thiamethoxam residues of concern were not adequately recovered by any of the tested multi-residue method protocols.

Based on the data collection method results, the QuEChERS multi-residue method may be suitable for enforcement.

2.2.2 Recommended Tolerances

Pending submission of a revised Section F (to propose a tolerance in imported whole bananas that is in accordance with HED's recommendation), there are no residue chemistry issues that would preclude the establishment of a tolerance in imported whole bananas at the level recommended by HED.

TABLE 2.2.2 Tolerance Summary for Thiamethoxam (40CFR §180.565[a]).

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)*	*Correct Commodity Definition*; Comments
Banana	0.04	0.03	Based on the banana field trial data submitted by Syngenta.

* Tolerance level as recommended by HED.

The currently established tolerance expressions for thiamethoxam (40CFR §180.565) are adequate, and include both coverage and compliance statements for enforcement purposes.

2.2.3 Revisions to Petitioned-For Tolerances

The petitioner should submit a revised Section F (to propose a tolerance in imported whole bananas that is in accordance with HED's recommendation of 0.03 ppm).

The submitted banana field trial data support a tolerance of 0.03 ppm, instead of the proposed tolerance of 0.04 ppm, in whole bananas. The petitioner used a combined limit of quantitation (LOQ) different from that used by HED for the input dataset of the Organization for Economic Cooperation and Development (OECD) tolerance calculation procedure. The combined LOQ used by HED resulted in a recommended tolerance of 0.03 ppm.

2.2.4 International Harmonization

Codex has established an MRL for thiamethoxam in bananas at 0.02 mg/kg. Canada's Pest Management Regulatory Agency (PMRA) has not established an MRL for thiamethoxam in bananas. Since the Codex and EPA residue definitions are different (Codex's MRL is for the parent compound, thiamethoxam only, while EPA's is thiamethoxam plus metabolite CGA-322704), it is not possible to harmonize HED's recommended tolerance with the Codex MRL.

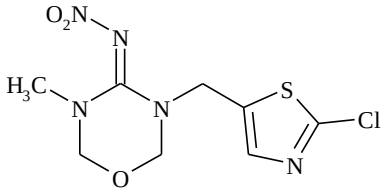
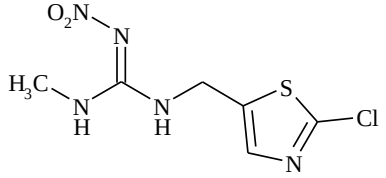
2.3 Label Recommendations

None.

3.0 Introduction

3.1 Chemical Identity

The nomenclature for thiamethoxam is presented in Table 3.1 below.

Table 3.1. Thiamethoxam Nomenclature.	
Chemical structure	
Empirical Formula	$C_8H_{10}ClN_5O_3S$
Common name	Thiamethoxam
Company experimental name	CGA 293343
IUPAC name	3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine
CAS name	3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-N-nitro-4H-1,3,5-oxadiazin-4-imine
CAS registry number	153719-23-4
End-use products (EP)	10% ai WDG (Actara or Reason). Tolerance without US registration.
Chemical Class	Neonicotinoid, IRAC Group 4A
Known Impurities of Concern	None
Chemical structure of CGA-322704 metabolite	 N-[(2-chloro-5-thiazoyl)methyl]-N'-methyl-N"-nitroguanidine
Common Name	Clothianidin

3.2 Physical/Chemical Characteristics

Thiamethoxam is a solid under ambient conditions and has low volatility. The compound has relatively low solubility in nonpolar organic solvents and its octanol/water partition coefficient suggest that accumulation of thiamethoxam in fatty tissues is unlikely to occur. The physicochemical properties are summarized in Appendix B.

3.3 Pesticide Use Pattern

The end-use product (EP), Solvigo 10.8 SC, is formulated as a suspension concentrate (SC) end-use product containing 7.15% thiamethoxam by weight, and 3.57% abamectin by weight. Only the active ingredient (ai) thiamethoxam is considered in this document. The use directions are summarized in Table 3.3, below.

TABLE 3.3 Summary of Thiamethoxam Directions for Use on Bananas						
Application Type; Timing; Equipment	**End-Use Product**	**Use Rate (lb ai/A)**	**Max. Uses per Season**	**Max. Seasonal Use Rate (kg ai/ha) [lb ai/A])**	**PHI (Days)**	**Use Directions and Limitations**
Foliar broadcast; and soil directed ground equipment and handheld backpack and motorized mist blower	Solvigo 10.8 SC	0.13	NS[4] 4-5 at trial sites	NS 7.20-1.152 [0.64-1.03] at trial sites	0	Spray volume not specified. 650-712 L/ha (69.5-76.1 GPA) were the spray volumes used at the trial sites.

PHI = Pre-Harvest Interval.
NS = Not Specified
GPA = gallons per acre

3.3 Anticipated Exposure Pathways

The Registration Division has requested an assessment of human health risk to support the establishment of a tolerance for residues of thiamethoxam in/on imported bananas. A domestic registration on bananas has not been requested. Humans may be exposed to thiamethoxam in imported food, since thiamethoxam may be applied directly to growing crops. There are no new residential uses of thiamethoxam, but there are existing exposures in residential and/or non-occupational settings; exposures via the dermal and inhalation routes are expected, and incidental oral exposure is expected for children. Since this action is for imported bananas only, U.S. occupational applicators will not be exposed via the dermal and inhalation routes while handling and applying thiamethoxam. There will also be no potential for dermal post-application exposure for workers re-entering treated fields.

Risk assessments have been previously prepared for the existing uses of thiamethoxam. This risk assessment considers the potential increased dietary exposure from thiamethoxam on bananas, but also considers the existing uses as well. A separate dietary exposure and risk assessment, as well as an updated aggregate risk assessment, was performed for CGA-322704 (clothianidin), taking into account the existing uses as well as the potential for CGA-322704 (clothianidin) residues in bananas as a result of application of thiamethoxam (D436256, J. Cowins, June 16, 2016).

3.4 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf. As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of

Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for children, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The toxicological database for thiamethoxam is complete and acceptable for selecting toxicity endpoints and points of departure for the purposes of human health risk assessment. An inhalation toxicity study is not available for thiamethoxam; however, HASPOC recommended, based on a WOE approach, that the study is not required (TXR# 0052354).

The available toxicology studies include the following:

- subchronic oral toxicity studies in rats, mice and dogs
- 28-day dermal toxicity study in rats
- developmental toxicity studies in rats and rabbits
- 2-generation reproduction studies in rats
- chronic toxicity studies in rats and dogs
- carcinogenicity studies in mice and rats
- battery of genotoxicity studies
- dermal penetration study in rats
- acute and subchronic neurotoxicity studies in rats
- developmental neurotoxicity study in rats
- immunotoxicity study in mice
- multiple ADME studies in rats and mice
- acute oral, dermal, and inhalation toxicity studies
- primary eye and dermal irritation studies
- dermal sensitization study
- non-guideline mechanistic studies to support the mode of action for carcinogenicity

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

The ADME of thiamethoxam was evaluated in both rats and mice and the results from both species were similar. In rats, thiamethoxam was rapidly and extensively absorbed, widely

distributed, and rapidly eliminated. There were no differences observed in absorption, distribution, or elimination between sexes, low or high doses, single or repeated dosing, or the position of the radiolabel in metabolism studies. The percentage of absorbed dose was estimated at ~90% of the administered dose (AD) based on values in urine, bile, and carcass at 48 hours post dose. Plasma concentrations in the blood were proportional between the low (0.5 mg/kg) and high (100 mg/kg) doses, indicating absorption was not saturated within that range. The highest tissue concentrations were in skeletal muscle (10-15% AD) at 2 hours post dosing and decreased to 0.12% AD by 24 hours; all other tissues examined were generally below 2% of the AD at 2 hours. Maximum blood concentrations were achieved within 1-4 hours of an oral dose, and the elimination half-lives were ~7 hours from blood and ~4 hours from tissues. Very low residues in tissue were reported after 7 days. Within 24 hours, approximately 84-95% of the administered dose was excreted in urine, while 2.5-6% was excreted in the feces. Most was excreted as unchanged parent (70-80% AD). The major biotransformation reaction is cleavage of the oxadiazine ring to form the corresponding nitroguanidine compound CGA-322704 (clothianidin). Enterohepatic circulation is negligible.

In a 14-day repeated-dose study in the mouse, approximately 72% of the administered dose was excreted in the urine and 19% was excreted in feces; bile cannulation experiments were not performed in mice. This supports that at least 72% of the AD was absorbed. No tissue distribution data were available in the mouse. Parent (33-41% AD) and two metabolites, CGA-322704 (8-12% AD) and a demethylation product of CGA-322704 (9-18% AD) were the only major metabolites identified. These are the same metabolites as observed in rat excreta; however, the proportions were different in the mouse. Pretreatment with thiamethoxam did not impact the relative fraction of metabolites observed in rats or mice, indicating that species differences are not due to the induction of metabolizing enzymes.

4.2.1 Dermal Absorption

HED recommends use of a 5% dermal absorption factor for risk assessment based on a weight of the evidence approach considering the following:1) both *in vivo* dermal absorption studies support that the dose remaining at the skin site is not available for continued absorption over time, 2) the highest percentage of dermal absorption across both *in vivo* rat studies was 4.22%, which is likely a conservative estimate due to the potential for oral exposure in that study, 3) the physical chemical properties (Log Kow <1) support a low dermal absorption, and 4) the NIOSH finite dose skin permeation calculator supports that dermal absorption is negligible in humans (see Appendix A.3).

4.3 Toxicological Effects

Thiamethoxam is a broad spectrum insecticide which belongs to the neonicotinoid class of compounds. Neonicotinoids act agonistically on the insect acetylcholine receptors (nAChR). Thiamethoxam itself has poor binding affinity for this receptor, although the major metabolite of thiamethoxam, CGA-322704 (clothianidin) has high affinity for insect nAChR[2]. Thiamethoxam also had essentially no affinity for the mammalian nicotinic acetylcholine receptor and was

[2] R. Nauen, et al. (2003). *Pesticide Biochemistry and Physiology*, 76(2):55-69

considered inactive in an *in vitro* nicotinic receptor binding study conducted by the registrant. No further studies were conducted to elucidate the mammalian mode of action.

CGA-322704 is a major metabolite of thiamethoxam and is also a registered pesticide. There are a number of similarities and differences between the toxicity profiles of the two chemicals, including the differences in the affinity for the nAChR receptor described earlier in this section. In general, CGA-322704 targets the hematopoietic system in dogs and the liver following chronic exposure in rats. This is similar to the organs affected by thiamethoxam. Also similar to thiamethoxam, CGA-322704 results in evidence of neurotoxicity following acute but not subchronic exposure. Tubular atrophy or germ cell loss in the testes was not observed in the CGA-322704 toxicity database. The only effect on sperm/testes observed in the CGA-322704 database was decreased sperm motility in the F_0 and F_1 generations of the two-generation reproduction study. For a full description of the toxicity profile of CGA-322704 please see the 2012 human health risk assessment (D397227; M. Doherty, 8/28/2012).

The available database of guideline studies for thiamethoxam indicates that the primary targets of toxicity are the liver, testes, adrenal glands, and the hematopoietic system.

Acute Toxicity
In acute lethality studies, technical thiamethoxam is slightly toxic to rats and moderately toxic to mice via the oral route of exposure (Toxicity Category III); it is of low toxicity to rats via the dermal (Toxicity Category III) and inhalation routes (Toxicity Category IV). It is not irritating to the skin and minimally irritating to the eye, and is not a dermal sensitizer.

Liver
Effects on the liver occurred in rats and mice and consisted primarily of increased liver weights, hepatocellular hypertrophy, and other histopathological changes such as lymphocytic infiltration, bile duct cholangiofibrosis, necrosis, and Kupffer cell pigmentation. In some studies these effects were accompanied by changes in clinical chemistry parameters, such as increased cholesterol, aspartate aminotransferase (AST), alkaline phosphatase (AP), or gamma-glutamyl transpeptidase (GGT). Across all studies, the effects on the liver did not seem to progress with time; effects on the liver were found at similar doses across both short- and long- term studies.

Testes
Effects on the testes were observed in both 2-generation reproduction studies in rats and all of the studies conducted in dogs. This included tubular atrophy of the testes in F_1 males in one study (MRID 44718707) and increased germ cell loss in F_1 males in a second study (MRID 46402904). While the effects observed in the two studies differ in description, the findings are consistent with respect to the testes as a target organ. Effects on the testes were not seen in any of the other rat studies. In the dog, effects on the testes were identified in both short- and long-term studies. The effects observed included decreased testicular weight, increased incidence of tubular atrophy, reduced spermatogenesis, and the occurrence of spermatic giant cells. It appeared that there may be some progression of toxicity in dogs as tubular atrophy occurred at a lower dose in the chronic study (21 mg/kg/day) as compared to the 90-day dog study (55 mg/kg/day). Testicular effects in dogs occurred at higher doses than rats in one reproduction study and at lower doses than rats in the other reproduction study.

Adrenal Gland
The effect on the adrenal gland was seen primarily in short-term rat studies and consisted of a fatty change of the adrenal cortex. The fatty change was seen in the 28-day dietary, 28-day gavage, and 90-day dietary rat studies. The effect was seen at a lower dose in the 90-day rat study compared to the 28-day studies; however, the effect was not observed following chronic exposure in rats up to 155 mg/kg/day.

Hematopoietic System
Effects on the hematopoietic system were seen in mice, rats, and dogs with the dog being the most sensitive species. Hematology effects were only seen in subchronic studies. The most common effects observed were leukopenia (dogs), changes consistent with microcytic anemia (dogs and mice), increased prothrombin time (dogs), and increased platelets (mice and rats).

Kidney
Effects on the kidney were seen in most of the rat studies. The effects were observed in male rats only and consisted primarily of hyaline change in tubular epithelium, basophilic proliferation of renal tubules, renal pelvic dilation, lymphocytic infiltration, and renal tubular casts. Monoclonal anti- α_{2u}-globulin immunohistochemical/hematoxylin staining was used on tissue samples from the 28-day, 90-day, and chronic rat studies. All three studies showed an increased staining in treated animals in the P_1 and P_2 regions of the renal cortex. The immunohistological staining and toxicity effects observed are consistent with α_{2u}-globulin induced nephrotoxicity, which is a male rat specific process that is not relevant for human health risk assessment (USEPA 1991).

Clinical Chemistry
Other effects commonly observed in rats and dogs included changes in clinical chemistry parameters and decreased body weights, both of which were sometimes seen at the LOAELs in subchronic and chronic studies. Altered clinical chemistry parameters included increased cholesterol and AST (rats), increased urea (dogs and rats), and increased creatinine (dogs and rats).

Neurotoxicity
Evidence of neurotoxicity was observed in the acute and developmental neurotoxicity studies. In the acute neurotoxicity (ACN) study, drooped palpebral closure, lower rectal temperature, increased forelimb grip strength (males only) and decreased locomotor activity were observed 2-3 hours after dosing at the lowest observed adverse effects level (LOAEL). Additional and more severe effects were seen at the next highest dose level. In the developmental neurotoxicity (DNT) study, there was no evidence of neurotoxicity in the dams. In contrast, there were statistically significant reductions in absolute brain weight and size (*i.e.*, length and width of the cerebellum was less in males on day 12, and there were significant decreases in different cross-sections of the microscopic evaluation of the brain (Level 3-5 in males and in Level 4-5 in females on Day 63) in pups. No treatment-related neurological effects were observed in the subchronic neurotoxicity study or in the rest of the database except for an increase in the incidence of hydrocephalus and pressure atrophy in the brain of high dose males in the rat chronic/carcinogenicity study, which was considered secondary to a pituitary adenoma.

In the rat developmental neurotoxicity study, there was evidence of quantitative susceptibility; effects in the pups (reduced brain weight and significant changes in brain morphometric measurements) were observed in the absence of adverse effects in dams. There was also evidence of quantitative susceptibility in both 2-generation reproduction studies; decreased pup body weights and testicular effects were observed in both studies despite no adverse toxicological effects relevant for risk assessment observed in parental animals. No evidence of increased quantitative or qualitative susceptibility was seen in the developmental toxicity studies in rats and rabbits. In the rat developmental study, skeletal anomalies were observed in the presence of maternal decreased body weight. In the rabbit developmental study, decreased fetal weight, increased post implantation loss, and skeletal variations and anomalies were observed in the presence of decreased body weight and bloody discharge in the perineal area in maternal animals.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

HED recommends that the FQPA SF of 10X be reduced to 1X based on the following considerations: (1) the completeness of the toxicity database including adequate studies to assess the potential susceptibility in the young (including a developmental neurotoxicity study); (2) there is no indication of quantitative or qualitative susceptibility in the developmental toxicity studies; (3) clear NOAELs were identified for the susceptibility in the 2-generation reproduction and DNT studies; (4) the endpoints and doses chosen for risk assessment are protective of the susceptibility observed in these studies; and (5) the endpoints chosen for risk assessment are protective of the potential neurotoxicity seen in the ACN study. Furthermore, HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

No additional factors are required to protect for the lack of an inhalation study. The lung does not appear to be a target organ based on acute inhalation and other neonicotinoid insecticides. The HASPOC (TXR# is 0056482) recommended, based on a WOE approach, that a 28-day inhalation toxicity study is not required for thiamethoxam. This recommendation is based on: (1) the use of an oral POD that results in MOEs > 1,000 for all exposure scenarios, except mixing/loading for application to sod farms, mixing/loading/applying for crack and crevice application, and primary seed treatment of cotton seeds in a closed system. These MOEs are considered conservative based on the inputs of amount treated; (2) the lung is not the target organ of thiamethoxam toxicity and no adverse respiratory effects were observed in the acute inhalation toxicity study; (3) the current POD for risk assessment is protective of testicular effects observed in subchronic oral toxicity studies; and (4) other chemicals similar to thiamethoxam do not demonstrate respiratory toxicity.

4.4.1 Completeness of the Toxicology Database

The toxicology database is considered complete and is adequate for the purpose of assessing pre- and postnatal susceptibility. Acceptable guideline studies for developmental, reproductive toxicity and neurotoxicity (including DNT) are available for FQPA assessment.

4.4.2 Evidence of Neurotoxicity

Evidence of neurotoxicity was seen in the acute and developmental neurotoxicity studies. There is a low degree of concern for the potential neurotoxic effects of thiamethoxam since clear no observed adverse effect levels (NOAELs) were identified for the neurotoxic effects, the neurotoxic effects were not the most sensitive endpoint in the toxicity database and the endpoints chosen for risk assessment are protective of any potential neurotoxicity.

4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

In the developmental studies, there was no evidence of increased quantitative or qualitative susceptibility of rat or rabbit fetuses to *in utero* exposure to thiamethoxam. Effects in the young were seen in the presence of maternal toxicity. There was evidence of quantitative susceptibility in the developmental neurotoxicity study and both two-generation reproductive studies. Although there was evidence of increased quantitative susceptibility, there are no residual uncertainties with regard to pre- and/or postnatal toxicity following *in utero* exposure to rats or rabbits and pre and/or post-natal exposures to rats. Considering the overall toxicity profile and the doses and endpoints selected for risk assessment, the degree of concern for the effects observed in the studies is low because the developmental/offspring effects observed in the studies are well characterized and clear NOAELs/LOAELs have been identified in the studies for the effects of concern. Additionally, the Agency is confident that the endpoints and PODs selected for risk assessment are protective of potential developmental/reproductive effects.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with respect to dietary, residential, or occupational exposure. The dietary exposure assessments are based on high-end, residue levels and processing factors, both of which account for parent and metabolites of concern, and the assumption that 100% of the crop is treated (for all registered crops). Actual risk from exposure to thiamethoxam will likely be much lower than HED's risk estimates conducted for the proposed import tolerance and existing uses. Furthermore, conservative, upper-bound assumptions were used to determine exposure through drinking water, such that these exposures have not been underestimated.

The residential exposure estimates are conservative and do not under-estimate exposure or risk.

4.5 Toxicity Endpoint and Point of Departure Selections

Based on the use pattern and the toxicological profile of thiamethoxam, HED selected endpoints and doses for acute and chronic dietary risk assessment and non-occupational exposures (i.e., incidental oral, dermal, or inhalation).
No new toxicity data have been received for thiamethoxam since the previous risk assessment (D425511, D. McNeilly et al., 7/2/2015). Upon review of the endpoints chosen for risk assessment, it was determined that for some studies, the toxicological effects reported at the LOAELs would not be considered adverse based on current approaches in hazard evaluation. However, these studies were not re-evaluated because the selected endpoints are protective of all the effects observed in the database and risks of concern that would require further refinement of

the toxicity endpoints were not identified. A number of the rat studies were updated to remove the kidney effects from the LOAELs because they were related to accumulation of α_{2u}-globulin and, therefore, are not relevant for human health risk assessment (USEPA 1991).

All endpoints selected for risk assessment remain the same as in the previous risk assessment, except for incidental oral and inhalation exposure. HED updated the incidental oral assessment (from the 90 day dog to the 28 day dog) and chose an inhalation endpoint specific for children <6 years old to refine the risk assessment for exposure to children. The choice of endpoints specific for children <6 years old for incidental oral, dermal and inhalation exposure were done as refinements because short-term exposure estimates exceeded the level of concern using the conservative endpoint of testicular effects that would not affect sexually immature children.

4.5.1 Dose-Response Assessment

Acute Dietary Endpoint (All Populations): The endpoint used for establishing the acute population-adjusted dose (aPAD) for the general population was selected from the developmental neurotoxicity study in the rat. An aPAD of 0.35 mg/kg/day was derived from a NOAEL of 34.5 mg/kg/day and a 100-fold factor that included 10x for inter-species extrapolations, 10x for intra-species variations, and a 1x FQPA SF. The LOAEL of 298.7 mg/kg/day was based on delayed sexual maturation in male pups and reduced brain morphometric measurements. This endpoint is appropriate for the acute dietary exposure assessment because the change in brain morphometrics could be the result of a single exposure at a critical junction during pregnancy or from multiple exposures throughout pregnancy, it is an appropriate route of exposure (oral), and it is protective of developing offspring. Furthermore, the selection of the developmental toxicity is protective of effects observed after a single dose in the acute neurotoxicity study.

Chronic Dietary (All Populations): The endpoint used for establishing the chronic population-adjusted dose (cPAD) was selected from the 2-generation reproduction studies in the rat. A cPAD of 0.01 mg/kg/day was derived from a NOAEL of 1.2 mg/kg/day (MRID 46402904; 2004 study) and a 100-fold factor that included 10x for inter-species extrapolation, 10x for intra-species variability, and a 1x FQPA SF. The LOAEL of 1.8 mg/kg/day (MRID 44718707; 1998 study) was based on testicular effects in the F_1 males. The NOAEL from this study was 0.6 mg/kg/day; however, the dose of 1.2 mg/kg/day from the second 2-generation reproduction study was used as the NOAEL based on the fact that there was no effect on the testes at this dose (testicular effects in this study were seen at 156 mg/kg/day). The NOAEL of 1.2 mg/kg/day from the 2004 study is considered protective of the effects observed at the LOAEL of 1.8 mg/kg/day in the 1998 study because the testicular effects observed in the 1998 study were considered conservative based on the marginal nature of the effect at the LOAEL and the effects were not corroborated in the other studies in the database. However, the Agency concluded that the LOAEL for testicular effects in the 2004 study could be used over the 1998 study, primarily because the two studies used different terminology, criteria, and scoring for the histopathological evaluation leading to uncertainty in comparing the results across studies.

The endpoint is based on the most sensitive effect observed in the database and is protective of *in utero* and developmental effects that could be associated with exposure to developing children.

Furthermore, the effect is protective of all the other effects observed in the toxicity database regardless of exposure duration or species. While a chronic dietary endpoint specific for children <6 years old could have also been chosen, this level of refinement was not necessary from a risk assessment perspective as the use of the current testicular effects is conservative and protective and does not result in any risks of concern.

Incidental Oral (Short-term): The endpoint used for assessing short-term incidental oral exposure was selected from the 28-day oral toxicity study in the dog. The NOAEL is 31.6 mg/kg/day, and the LOC is 100 (10x for inter-species extrapolation, 10x for intra-species variability, and a 1x FQPA SF). The effects observed at the LOAEL of 43.0 mg/kg/day were decreased body weight, changes in hematopoietic and clinical chemistry parameters, and histopathological changes in the liver, thymus, and spleen. The study, dose and endpoint were selected because the study is of the appropriate route and duration and is protective of all offspring effects in the reproduction and developmental studies. Based on a weight of the evidence approach, the effects on the testes observed in the 2-generation reproduction studies were not considered appropriate for children under the age of six and were not chosen for this scenario. This approach considered the following: 1) the effects in the 2004 2-generation reproduction study (MRID 46402904) were primarily observed adjacent to the rete testis. The rete testis is a structure where the seminiferous tubules empty sperm which are then concentrated as fluids are reabsorbed. Since decreased sperm counts were not observed in the seminiferous tubules, this supports the concept that the germ cell loss was not due to damage to the spermatogonia, spermatocytes, or spermatids (initial cell types in the spermatogenesis pathway) *per se* but rather to an effect of the transit of spermatids between the seminiferous tubule and the rete testis. 2) In humans spermatogenesis begins at puberty. Since the data support that thiamethoxam is affecting transit from the seminiferous tubule into the rete testis and not the precursor cells, children would not be susceptible to the effects until spermatogenesis begins. 3) the effects on the testes were only observed in the F_1 generation of both 2-generation reproduction studies which could imply a developmental effect. However, tubular atrophy was also observed in the 90-day and 1-year dog studies, indicating that exposure to thiamethoxam can cause testicular effects in animals that did not receive developmental exposure. This further supports that thiamethoxam is exerting its effect on cells/tissues that are involved in the maturation of spermatids as they traverse through the male reproductive tract and not the production of sperm cells, and 4) No developmental delays were observed in the toxicity database, including two developmental studies (rat and rabbit) and both two generation reproduction studies.

Dermal – Adults (Short-Term): The endpoint used for establishing the dermal exposure for adults was selected from two co-critical 2-generation reproduction studies in the rat. The NOAEL is 1.2 mg/kg/day, and the LOC is an MOE of 100 (10x for inter-species extrapolation, 10x for intra-species variability, and a 1x FQPA SF). The testicular effects and LOAEL have been described above (see chronic dietary). Although a 28-day dermal toxicity study in rats is available, HED selected a reproductive NOAEL to protect for the effects observed in the reproduction study that were not evaluated in the dermal toxicity study. Since an oral toxicity study was selected, the 5% dermal absorption factor from the rat dermal absorption study is recommended.

Dermal – Children Age 1 to 6 years (Short-Term): The endpoint used for assessing dermal exposure to children <6 years of age was selected from the 28-day dermal study in rats. The NOAEL is 60 mg/kg/day, and the LOC is a MOE of 100 (10x for inter-species extrapolation, 10x for intra-species variability, and a 1x FQPA SF). The LOAEL of 250 mg/kg/day is based on increased plasma glucose, triglyceride levels, and alkaline phosphatase activity as well as inflammatory cell infiltration in the liver and necrosis of single hepatocytes in females. The Agency selected the dermal toxicity study to assess young children because the testicular effects observed in the two-generation rat reproduction study are not relevant for young children that are sexually immature. Because a route-specific toxicity study was selected, a dermal absorption factor is not necessary when assessing dermal exposure to children.

Inhalation - Adult (Short-Term): The endpoint used for assessing inhalation exposure to adults was selected from two co-critical 2-generation reproduction studies in the rat. The NOAEL is 1.2 mg/kg/day, and the LOC is an MOE of 100 (10x for inter-species extrapolation, 10x for intra-species variability, and a 1x FQPA SF). The effects observed and the LOAEL have been described above (see chronic dietary). These studies was selected because of the exposure duration, and because the endpoint (testicular effects) is protective of all other effects in the database. No route-specific repeat dose study is available to assess potential inhalation toxicity resulting from thiamethoxam exposure. In the absence of a route-specific study, the NOAEL and LOAEL from an oral study have been used for risk assessment (i.e., inhalation toxicity is assumed to be equivalent to oral toxicity).

Inhalation – Children <6 years (Short-Term): The endpoint used for assessing short-term inhalation exposure to children <6 years of age was selected from the 28-day oral toxicity study in the dog. The NOAEL is 31.6 mg/kg/day, and the LOC 100 (10x for inter-species extrapolation, 10x for intra-species variability, and a 1x FQPA SF). The effects and LOAEL have been described above (see incidental oral). The study, dose and endpoint were selected because the study is of the appropriate duration and is protective of all offspring effects in the reproduction and developmental studies. The Agency selected the 28-day dog study to assess young children because the testicular effects observed in the two-generation rat reproduction study are not relevant for young children that are sexually immature (see the incidental oral endpoint for a more detailed rationale). No route-specific information is available for the inhalation toxicity of thiamethoxam. In the absence of a route-specific study, the NOAEL and LOAEL from an oral study have been used for risk assessment (i.e., inhalation toxicity is assumed to be equivalent to oral toxicity).

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

For adults, the same endpoint (testicular effects) and dose were selected for exposures via the dermal and inhalation routes, so they have been combined in the risk assessment. For children, the liver was the target following oral, dermal, and inhalation exposure, so these routes may be combined.

4.5.3 Cancer Classification and Risk Assessment Recommendation

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC re-classified thiamethoxam as **"Not Likely to be Carcinogenic to Humans"** based on convincing evidence that a non-genotoxic mode of action for liver tumors was established in the mouse and that the carcinogenic effects are a result of a mode of action dependent on sufficient amounts of a hepatotoxic metabolite produced persistently. Although humans are qualitatively capable of producing the active metabolite, thiamethoxam is unlikely to pose a cancer risk to humans unless sufficient amounts of metabolites are persistently formed to drive a carcinogenic response. Lastly, the non-cancer assessment is sufficiently protective of the key events (perturbation of liver metabolism, hepatotoxicity/regenerative proliferation) in the animal mode of action and, thus, cancer is not an issue. Thus, quantification of carcinogenic potential is not required.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Thiamethoxam for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary All populations including infants and children	NOAEL = 34.5 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF=1	aRfD=0.35 mg/kg/day aPAD=0.35 mg/kg/day	**Rat Developmental Neurotoxicity study** LOAEL = 298.7 mg/kg/day based on decreased body weight and reduced brain morphometric measurements.
Chronic Dietary All populations including infants and children	NOAEL= 1.2 mg/kg/day (MRID 46402904)	UF_A= 10x UF_H= 10x FQPA SF =1	cRfD=0.012 mg/kg/day cPAD=0.012 mg/kg/day	**2-Generation reproduction study (MRID 44718707)** LOAEL = 1.8 mg/kg/day based on increased incidence and severity of tubular atrophy in testes of F_1 generation males. **2-Generation reproduction study (MRID 46402904)** LOAEL = 156 mg/kg/day (males), not determined (females) based on sperm abnormalities and germ cell loss in F_1 males.

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Thiamethoxam for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral (Short-term) (infants/ children <6 yrs)	NOAEL= 31.6 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF =1	MOE= 100 (residential)	**28-day Dog study (MRID 44703324)** LOAEL = 47.7/43.0 (M/F) mg/kg/day based on body weight loss; leukopenia and increased hematocrit, hemoglobin and erythrocyte count; increased plasma urea and creatinine; reduced thymus weight in males and females, increased thyroid weight in males and reduced brain weight in females; and, histopathological changes in liver, thymus and spleen.
Dermal (Short-term) (Adults)	Oral study NOAEL= 1.2 mg/kg/day (MRID 46402904) (Dermal Absorption = 5%)	UF_A= 10x UF_H= 10x FQPA SF =1	MOE= 100 (residential)	**2-Generation reproduction study; 1998. (MRID 44718707)** LOAEL = 1.8 mg/kg/day based on increased incidence and severity of tubular atrophy in testes of F_1 generation males. **2-Generation reproduction study; 2004. (MRID 46402904)** LOAEL = 156 mg/kg/day (males), not determined (females) based on sperm abnormalities and germ cell loss in F_1 males.
Dermal (Short-term) (infants/ children <6 yrs)	Dermal Study NOAEL=60 mg/kg/day	UF_A= 10x UF_H= 10x FQPA SF =1	MOE= 100 (residential)	**Rat 28-Day Dermal Toxicity Study (MRID 44710402)** LOAEL = 250 (females) mg/kg/day based on increased plasma glucose, triglyceride levels, and alkaline phosphatase activity and inflammatory cell infiltration in the liver and necrosis of single hepatocytes in females.
Inhalation (Short-term) (Adults)	Oral study NOAEL= 1.2 mg/kg/day (MRID 46402904) (inhalation toxicity = oral toxicity)	UF_A= 10x UF_H= 10x FQPA SF =1x	MOE= 100 (residential)	**2-Generation reproduction study (MRID 44718707)** LOAEL = 1.8 mg/kg/day based on increased incidence and severity of tubular atrophy in testes of F_1 generation males. **2-Generation reproduction study (MRID 46402904)** LOAEL = 156 mg/kg/day (males), not determined (females) based on sperm abnormalities and germ cell loss in F_1 males.

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Thiamethoxam for Use in Dietary and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation (Short-term) (infants/ children <6 yrs)	NOAEL= 31.6 mg/kg/day (inhalation toxicity = oral toxicity)	UF_A= 10x UF_H= 10x FQPA SF =1x	MOE= 100 (residential)	**28-day Dog study (MRID 44703324)** LOAEL = 47.7/43.0 (M/F) mg/kg/day based on body weight loss; leukopenia and increased hematocrit, hemoglobin and erythrocyte count; increased plasma urea and creatinine; reduced thymus weight in males and females, increased thyroid weight in males and reduced brain weight in females; and, histopathological changes in liver, thymus and spleen.
Cancer (oral, dermal, inhalation)	**"Not Likely to be Carcinogenic to Humans"** based on convincing evidence that a non-genotoxic mode of action for liver tumors was established in the mouse. Quantification of cancer risk is not required.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

MARC Decision Memo: D258614, 8/31/99, G.J. Herndon
Residue Chemistry Memo D252021, 3/30/00, G.J. Herndon
Residue Chemistry Memo D265079, 5/8/00, G.J. Herndon
Residue Chemistry Memo D281702, 4/17/07, M. Doherty

The residues of concern for thiamethoxam have not changed in the current assessment for bananas, and are described in Table 5.1.

Table 5.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression			
Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression for Compliance Monitoring
Plants	Primary Crop	Thiamethoxam + GCA-322704	Thiamethoxam + GCA-322704
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Thiamethoxam + GCA-322704	Thiamethoxam + GCA-322704
	Poultry	Thiamethoxam + GCA-322704	Thiamethoxam + GCA-322704
Drinking Water		Thiamethoxam	Not Applicable

5.2 Food Residue Profile

W. Drew, D429716, November 8 2016

Syngenta Crop Protection has submitted a petition (5E8401) requesting the establishment of a permanent tolerance (without US registration) for residues of thiamethoxam in bananas grown outside the US. There are no processed commodities associated with bananas. The dietary burden of thiamethoxam to livestock will not be affected by the proposed use, and the current tolerances in livestock commodities are adequate.

The data submitted in support of the current action (PP#5E8401) along with previously reviewed data, are adequate for the purpose of both risk assessment and tolerance assessment for the proposed use on banana. Maximum residues of thiamethoxam are expected to occur at relatively low levels (<0.03 ppm in both banana whole fruit and pulp), while CGA-322704 (clothianidin) residues are expected to be below the LOQ, for the use requested in the current petition. The submitted banana field trial data are adequate, and support the establishment of a permanent tolerance in imported banana whole fruit at 0.03 ppm.

The results from these field trials show that maximum combined residues of thiamethoxam and CGA-322704 in banana whole fruit and pulp were 0.0285 and 0.0255 ppm, respectively (in terms of thiamethoxam equivalents). The banana field trial residue results are summarized in Table 5.2.

TABLE 5.2 Summary of Residue Data from Banana Field Trials with Thiamethoxam.

Banana Matrix	Total Rate (g ai/ha) [lb ai/A])	PHI (Days)	Residue Levels (ppm)[1]							
			n	Min.	Max.	HAFT[2]	LAFT[2]	Median	Mean	Std. Dev.
Residues of CGA-322704[3]										
Whole fruit	720-1152 [0.64-0.103]	0	24	<0.010	<0.010	0.010	0.010	0.010	0.010	0
Pulp				<0.010	<0.010	0.010	0.010	0.010	0.010	0
Residues of Thiamethoxam[3]										
Whole fruit	720-1152 [0.64-0.103]	0	24	<0.010	0.0168	0.0164	0.010	0.010	0.0107	0.0019
Pulp				<0.010	0.0138	0.0138	0.010	0.010	0.0106	0.0013
Combined Residues of Thiamethoxam and CGA-322704[4]										
Whole fruit	720-1152 [0.64-0.103]	0	24	<0.0217	0.0285	0.0281	0.0217	0.0217	0.0224	0.0019
Pulp				<0.0217	0.0255	0.0255	0.0217	0.0217	0.0223	0.0013

1. For n, minimum and maximum, individual sample residues were used; for HAFT, LAFT, median, mean and standard deviation, average trial residues were used.
2. HAFT = Highest Average Field Trial; LAFT = Lowest Average Field Trial.
3. For individual residues <LOQ, the LOQs (0.010 ppm for both thiamethoxam and CGA-322704) were used in calculations.
4. For combined residues <LOQ, the combined LOQ (0.010 ppm for thiamethoxam + 0.0117 ppm for CGA-322704 in terms of parent equivalents = 0.0217 ppm) was used in calculations. All CGA-322704 residues were <LOQ, so were assumed to be 0.0117 ppm

5.3 Water Residue Profile

Reference: EFED Memo D373378, C. Koper, 20 May 2010
EFED Memo D391528, C. Koper, 28 July 2011

The estimated drinking water concentrations (EDWCs) in the dietary risk assessment were provided by Environmental Fate and Effects Division (EFED) (D391528, C. Koper, 28 July 2011 and D373378, C. Koper, 20 May 2010) and remain unchanged since the last risk assessment, because this is not a domestic use. The EDWCs were directly incorporated into the DEEM-FCID™ dietary assessments via entry into the food categories "water, direct, all sources" and "water, indirect, all sources." CGA-322704, a major metabolite of thiamethoxam in plants and livestock, is not a significant degradate of thiamethoxam in surface or groundwater sources of drinking water. As a result, CGA-322704 residues are not included in the EDWCs.

For surface water, the EDWCs for the crops evaluated/modeled in this assessment did not exceed the EDWCs for rice reported in the previous drinking water assessment (D363202, F. Khan, 07 April 2009). The reported acute concentration of 131.77 µg/L, annual mean (chronic) concentration of 11.31 µg/L, and the highest 30 year annual average concentration of 11.31 µg/L from the rice model are higher than the reported EDWCs for the other modeled uses (surface water from cranberry and groundwater from dry bulb onions. Therefore, the EDWCs generated by the Rice Model were used. The drinking water models and their descriptions are available at the EPA internet site: Models for Pesticide Risk Assessment.

A summary of the estimated drinking water concentrations for thiamethoxam are presented in Table 5.3.

Table 5.3. Tier II Estimated Drinking Water Concentrations (EDWCs) resulting from applications of Thiamethoxam.

Drinking Water Source (model)	Use Scenario (modeled rate)	Acute EDWC (µg/L)	Chronic EDWC (µg/L)
Tail water (Rice Model)	Rice (0.173 lbs ai/A/year)	**131.77**[1,2]	**11.31**[1,3]
	Cranberry (0.188 lbs ai/A/year)	54.75[2]	4.50[3]
Groundwater (SCI-GROW)	Dry bulb onions: (1 app. X 0.30 lbs. ai/acre)	4.66	4.66
Bold text denotes maximum estimated EDWC values. All values adjusted with PCA factor of 0.87.			

[1] Recommended EDWCs for surface water.
[2] EDWCs based on day 1.
[3] EWDCs based on average of 365 days.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

The USDA Pesticide Data Program (PDP) monitored pesticide residues in catfish in 2008, 2009, and 2010 and residues in salmon in 2013 and 2014. Over this period, PDP analyzed 1479 samples of catfish and 677 samples in salmon for thiamethoxam residues. None of the samples contained detectable residues. As a result, residues in fish were not included in the assessment.

The acute assessment is based on tolerance level residues of thiamethoxam/ CGA-322704 (the tolerance is for combined residues). The chronic analysis is based on tolerance level/proposed tolerance levels and/or average field trial residues (D429716, W. Drew, November 8, 2016), and assumes 100% crop treated for all included commodities.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The dietary assessment is a screening-level assessment using tolerance level residues for the acute analysis. Tolerance levels and anticipated residues (calculated from field trial data) for selected commodities (discussed in detail in D408149, D. McNeilly, Jan 31, 2013) were used in the chronic assessment. The chronic assessment anticipated residues were average residues from crop field trial data. For both the acute and chronic analyses, 100% crop treated was assumed.

5.4.3 Acute Dietary Risk Assessment

The Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID), Version 3.16, which incorporates consumption data from the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (USDA's NHANES/WWEIA) analyses estimate the dietary exposure of the US population and various population subgroups. Based on highly conservative assumptions, acute dietary (food and water) risk estimates are less than or equal to 9.5% of the acute population-adjusted dose (aPAD) for all population subgroups (see Table 5.4.6). Generally, HED is concerned when risk estimates exceed 100% of the PAD; therefore, all acute dietary risk estimates are below HED's LOC.

5.4.4 Chronic Dietary Risk Assessment

Chronic dietary (food and water) risk estimates are less than or equal to 45% of the chronic population-adjusted dose (cPAD) for all population subgroups (Table 5.4.6). Generally, HED is concerned when risk estimates exceed 100% of the PAD; therefore, all chronic dietary risk estimates are below HED's LOC.

5.4.5 Cancer Dietary Risk Assessment

Thiamethoxam has been classified as "not likely to be carcinogenic to humans." As such, the risk of cancer from thiamethoxam is not of concern.

5.4.6 Summary Table

HED is concerned when risk estimates exceed 100% of the PAD. The population subgroup with the highest acute and chronic exposure estimates was children 1-2 years old. The risk estimates for the general U.S. population and all population subgroups are below HED's level of concern for both acute and chronic exposure durations as summarized in Table 5.4.6.

Table 5.4.6. Summary of Dietary (Food + Drinking Water) Exposure and Risk Estimates for Thiamethoxam.							
Population Subgroup[2]	aPAD, mg/kg/day	Acute Estimates (95th Percentile)[1]		cPAD, mg/kg/day	Chronic Estimates		
		Exposure, mg/kg/day	Risk, % aPAD		Exposure, mg/kg/day	Risk, % cPAD	MOE[3]
U.S. Population	0.35	0.017415	5.0	0.012	0.002778	23	11,000
All infants (< 1 year)[2]	0.35	0.028062	8.0	0.012	0.002608	22	12,000
Children 1-2 yrs	**0.35**	**0.033388**	**9.5**	**0.012**	**0.005400**	**45**	**5,900**
Children 3-5 yrs	0.35	0.027295	7.8	0.012	0.004551	38	6,900
Children 6-12 yrs	0.35	0.017659	5.1	0.012	0.002834	24	11,000
Youth 13-19 yrs	0.35	0.012888	3.7	0.012	0.002105	18	15,000
Adults 20-49 yrs	0.35	0.016421	4.7	0.012	0.002620	22	12,000
Adults 50-99 yrs	0.35	0.015830	4.5	0.012	0.002730	23	12,000
Females 13-49 yrs	0.35	0.016827	4.8	0.012	0.002699	23	12,000

1 - Results for the 99th and 99.9th percentile are reported in Attachment 2.
2 - The population subgroups used in the aggregate risk assessment are bolded.
3 - MOEs are based on the short-term incidental oral NOAEL of 31.6 mg/kg/day.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no new residential uses associated with this action; however, there are existing residential uses which were previously assessed and reflect updates to HED's 2012 Residential SOPs[3] along with a revision to the inhalation POD for children ≤ 6 years of age (D359207, M. Collantes, July 24, 2009; and D406746, M. Crowley, Dec 4, 2012). Residential exposures (handler and post-application) are anticipated based on the registered use pattern of thiamethoxam.

6.1 Residential Handler Exposure

Thiamethoxam has existing residential uses on turf and indoor environments (crack-and-crevice uses). **Table 6.1.a** provides a summary of the registered residential uses**.**

Table 6.1.a: Registered Residential Handler Scenarios for Thiamethoxam				
Formulation and Product	**Method of Application**	**Use Sites**	**Application Rate**	**Timing of Application**
Optigard ™ 21.6% liquid suspension concentrate	Manually pressurized handwand	Indoor Spot, Crack and Crevice	0.0084 lb ai/gal (0.0000042 lb ai/ft2)	NA

[3] Available: http://www.epa.gov/pesticides/science/residential-exposure-sop.html

Table 6.1.a: Registered Residential Handler Scenarios for Thiamethoxam				
Meridian ™ 25WG 25% ai water dispersible granule	groundboom, backpack, handwand	golf course, residential lawns, commercial grounds, athletic fields, playgrounds, and sod farms	Turf and soil – 0.198 to 0.266 lb ai/A Foliage of plants – 0.0003125 to 0.00133 lb ai/gal	Applied to turf grass, plant foliage and soil; max amount applied per growing season = 0.266 lb ai/A
Meridian ™ 0.33G 33% ai granule	Granular broadcast spreader	golf course, residential lawns, commercial grounds, athletic fields, and playgrounds	Turf - 0.1875– 0.248 lb ai/A Ornamentals - 0.022 lb ai/5,000 sq. ft. – 0.029 lb ai/5000 sq. ft.	Applied to turf grass and soil; max amount applied per growing season = 0.248 lb ai/A

No risk estimates of concern were identified for the residential handlers for the existing uses of thiamethoxam. A summary of the residential handler risk estimates is provided in Table 6.1.b

Table 6.1b. Residential Handler Non-cancer Exposure and Risk Estimates for Existing Residential Uses of Thiamethoxam.

Scenario	Formulation	Equipment	Dose (mg/kg-day)		MOE		
			Dermal[1]	Inhalation[3]	Dermal[2]	Inhalation[4]	Combined[5]
Lawns/Turf	WDG	Manually-pressurized handwand	0.00033	0.00011	3,600	11,000	2,700
		Backpack	0.00033	0.00011	3,600	11,000	2,700
	Granule	Rotary / push-type spreader	0.000073	0.0000047	16,000	260,000	15,000
		Belly grinder	0.0018	0.0000039	670	310,000	670
Indoor (crack-and-crevice)	Liquid	Manually-pressurized handwand	0.00021	0.000067	5,700	18,000	4,300

1 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled ÷ Body Weight (69 kg).
2 Dermal MOE = Dermal NOAEL (1.2 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
3 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) ÷ Body Weight (69 kg).
4 Inhalation MOE = Inhalation HED (1.2 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
5. Total MOE = NOAEL (1.2 mg/kg/day) ÷ (Dermal Dose mg/kg/day + Inhalation Dose mg/kg/day)

6.2 Post-Application Exposure

There is a potential for exposure from entering areas previously treated with thiamethoxam. The LOC for the margin of exposure (MOE) is 100 for all residential uses. All post-application scenarios associated with turf and indoor crack and crevice uses resulted in MOEs greater than 100 and are not of concern. A summary of the post-application exposure and risk estimates is provided in Table 6.2.

Table 6.2. Residential Post-application Non-cancer Exposure and Risk Estimates for Existing Residential Uses of Thiamethoxam.							
Use/Target	**Lifestage**	**Post-application Exposure Scenario**		**Dose (mg/kg-day)**	**MOE[3]**	**Combined Routes (X indicates included in Combined MOE)**	**Combined MOE**
Turf (spray application)[1]	Adult	Dermal	High-contact (playing)	0.0024	500	--	NA
			Mowing	0.000049	25,000	--	
			Golfing	0.00019	6,400	--	
	Child 11<16	Dermal	Mowing	0.000048	25,000		NA
			Golfing	0.00019	6,400	--	
	Child 6<11	Dermal	Golfing	0.00022	5,400	--	NA
	Child 1<2	Dermal (high-contact play)		0.082	740	X	640
		Hand to Mouth		0.0017	4,900	X	
		Object to Mouth		0.00005	160,000	--	
		Incidental Soil Ingestion		9.0E-06	910,000	--	
Indoor (crack-and-crevice)	Adult	Dermal (playing on carpet)[2]		0.00049	2,500	X	2,500
		Inhalation		9.1E-07	1,300,000	X	
	Child 1<2	Dermal (playing on carpet)[3]		0.0081	7,400	X	5,900
		Inhalation		3.4E-06	9,400,000	X-	
		Hand to Mouth (playing on carpet)[2]		0.0012	26,000	X	

[1] Risk estimates are based on the maximum day-of-application value from a submitted turf transferable residue study (MRID 46402915) conducted at the maximum application rate. Risks from liquid spray applications are presented and are considered health-protective of granule formulation uses as most measured TTR values for granule formulations were < LOD.
[2] Risk estimates presented in this table are from contacting treated carpets only; risks from contacting other surfaces are lower.
[3] MOEs are for short-term exposures only.

6.3 Residential Risk Estimates for Use in Aggregate Assessment

HED selected only the most conservative, or worst case, residential adult and child scenarios to be included in the aggregate estimates, based on the lowest overall MOE (i.e., highest risk estimates). The worst case residential exposures for adults and children 1 to 2 years old were associated with post-application exposure to treated turf. The adult dermal exposure estimate resulted in an MOE of 550. The child dermal exposure estimate resulted in a combined dermal and incidental oral MOE of 640. All scenarios resulted in MOEs greater than their respective LOCs (adult dermal and inhalation MOE $\geq$ 100; child dermal, inhalation and incidental oral MOE $\geq$ 100) and are not of concern. A summary of the residential exposures and risk estimates recommended for the aggregate assessment is provided in Table 6.3.

Table 6.3. Recommendations for the Residential Exposures for the Thiamethoxam Aggregate Assessment.[1]								
Lifestage	Handler Exposure (mg/kg/day)[2]		Residential Handler Total Exposure (mg/kg/day)[3]	Residential Handler Total MOE	Post-Application Exposure (mg/kg/day)[4]			Residential Post-application MOE[5]
	Dermal	Inhalation			Dermal	Inhalation	Oral	
Short-/Intermediate-Term								
Adult	0.0018	0.0000039	0.0018	670	0.0024	N/A	N/A	500
Child 1<2	N/A				0.082	N/A	0.0017	640

[1] Bolded risk estimates should contribute to the residential exposure portion of the aggregate assessment.
[2] Residential Handler Dose = the highest handler dose for each applicable lifestage of all scenarios assessed from Table 6.1 (i.e., belly grinder). Total = dermal + inhalation. [3] Residential Handler MOE = the MOEs associated with the highest doses identified in Table 6.1 (i.e., belly grinder). Total = 1/ (1/Dermal MOE) + (1/Inhalation MOE).
[4] Residential Post-application Dose = the highest post-application dose for each applicable lifestage of all scenarios assessed from Table 6.2 (adults: turf post-application; children 1< 2: turf post-application). Total = dermal + inhalation + incidental oral, where applicable.
[5] Residential Post-application MOE = the MOEs associated with the highest doses identified in Table 6.2 (adults: turf post-application; children 1< 2: turf post-application). Total = 1/ (1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental oral MOE).

6.4 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for thiamethoxam**.** The agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the agency's Spray Drift website for more information). [4] The agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift.* This document outlines the quantification of indirect non-occupational exposure to drift.

6.5 Non-Occupational Bystander Post-application Inhalation Exposure Resulting from Agriculture and Commercial Outdoor Uses

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219).

[4] Available: http://www2.epa.gov/reducing-pesticide-drift

During Registration Review, the agency will use this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for thiamethoxam.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

Note that because CGA-322704 (clothianidin) is a major metabolite of thiamethoxam, and there is no established tolerance for residues of CGA-322704 (clothianidin) in bananas, EPA has to consider the impact of thiamethoxam use on imported bananas on the CGA-322704 (clothianidin) risk estimates and is addressed in a separate risk assessment (D436256, J. Cowins, November 10, 2016).

7.1 Acute Aggregate Risk

In examining acute aggregate risk, HED has assumed that the only pathway of exposure relevant to that time frame is dietary exposure. Therefore, the acute aggregate risk is composed of exposures to thiamethoxam residues in food and drinking water and is equivalent to the acute dietary risk discussed in Section 5.4.6. As noted in that section, the acute risk estimates are well below HED's dietary level of concern for all population subgroups.

7.2 Short-Term Aggregate Risk

References: D375247, D. McNeilly, 3 May 2010
D359207, M. Collantes; 24 July 2009
D406746, M. Crowley, Dec 4, 2012

Short-term residential exposures (1 to 30 days of continuous exposure) to thiamethoxam may occur. Estimates indicate that the turf scenario has higher exposure for both adults and children than the exposure levels in indoor (crack and crevice) scenarios (Table 6.2) and that for adults, post-application exposure may be greater than handler exposure (Tables 6.1 and 6.2). Therefore, exposure estimates resulting from entering turf areas previously treated with a thiamethoxam product are the focus of the short-term aggregate risk estimates. Exposures related to turf activities (Table 6.3) have been combined with chronic dietary exposure estimates (as an estimate of background dietary exposure, Table 5.4.6) to assess the worst-case short-term aggregate exposure. The short-term aggregate MOEs range from 500 to 580 (Table 7.2). These aggregate risk estimates are greater than the LOC of 100 and therefore are not of concern.

Table 7.2. Estimates of Short-term Aggregate Risks for Thiamethoxam			
Population Subgroup	Margins of Exposure (MOEs)		
	Dietary Aggregate[1]	Residential Combined MOE[2]	Total Short-Term Aggregate [3]
Adult	11,000	500	500
Children 1<2 years of age	5,900	640	580

[1] Dietary Aggregate MOE = Incidental Oral NOAEL (31.6 mg/kg/day) ÷ Chronic Dietary (Food + Water) Exposure (mg/kg/day; from Table 5.4.6). Values are rounded to 2 significant figures.
[2] Turf exposure from Table 6.2.
[3] Total Aggregate MOE = $1/[(1/MOE_{Dietary}) + (1/MOE_{Residential\ Combined}))]$. Values rounded to 2 significant figures.

7.3 Intermediate-Term Aggregate Risk

Intermediate-term exposures (30 to 180 days of continuous exposure) are not expected from the turf and/or indoor residential uses of thiamethoxam.

7.4 Chronic Aggregate Risk

In examining chronic aggregate risk, HED has assumed that the only pathway of exposure relevant to that time frame is dietary exposure. Therefore, chronic aggregate risk is composed of exposures to thiamethoxam residues in food and drinking water and is equivalent to the chronic dietary risk discussed in Section 5.4.6. As noted in that section, the chronic risk estimates are below HED's dietary level of concern for all population subgroups.

7.5 Cancer Aggregate Risk

Thiamethoxam has been classified as "not likely to be carcinogenic to humans." As such, the risk of cancer from thiamethoxam is not of concern.

8.0 Cumulative Exposure/Risk Characterization

Thiamethoxam is a member of the neonicotinoid class of pesticides and produces, as a metabolite, another neonicotinoid, CGA-322704. Structural similarities or common effects do not constitute a common mechanism of toxicity. Evidence is needed to establish that the chemicals operate by the same, or essentially the same, sequence of major biochemical events (EPA, 2002). Although CGA-322704 and thiamethoxam bind selectively to insect nicotinic acetylcholine receptors (nAChR), the specific binding site(s)/receptor(s) for CGA-322704, thiamethoxam and the other neonicotinoids are unknown at this time. Additionally, the commonality of the binding activity itself is uncertain, as preliminary evidence suggests that CGA-322704 operates by direct competitive inhibition, while thiamethoxam is a non-competitive inhibitor. Furthermore, even if future research shows that neonicotinoids share a common binding activity to a specific site on insect nAChRs, there is not necessarily a relationship between this pesticidal action and a mechanism of toxicity in mammals. Structural variations between the insect and mammalian nAChRs produce quantitative differences in the binding affinity of the neonicotinoids towards these receptors which, in turn, confers the notably

greater selective toxicity of this class towards insects, including aphids and leafhoppers, compared to mammals. While the insecticidal action of the neonicotinoids is neurotoxic, the most sensitive regulatory endpoint for CGA-322704 is based on unrelated effects in mammals, including changes in body and thymus weights, delays in sexual maturation, and still births. Additionally, the most sensitive toxicological effect in mammals differs across the neonicotinoids (such as testicular tubular atrophy with thiamethoxam, and mineralized particles in thyroid colloid with imidacloprid). Therefore, unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to thiamethoxam and any other substances and thiamethoxam does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that thiamethoxam has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity, and to evaluate the cumulative effects of such chemicals, see the policy statements concerning common mechanism determinations, and procedures for cumulating effects from substances found to have a common mechanism, released by OPP on EPA's website at http://www.epa.gov/pesticides/cumulative/.

9.0 Occupational Exposure/Risk Characterization

Not applicable for a tolerance without a US registration.

10.0 References

References:

D436256, J. Cowins, November 10,2016, Thiamethoxam. Addendum to the HED Risk Assessment for Tolerances on Imported Bananas

D429717, J. Cowins, June 16, 2016, Thiamethoxam. Acute and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for Residues of Thiamethoxam on Imported Banana.

D429716, W. Drew, November 8, 2016, Thiamethoxam. Petition Proposing the Establishment of a Permanent Tolerance (Without Section 3 Registration) for Use of Insecticide on Imported Bananas. Summary of Analytical Chemistry and Residue Data.

D408149, D. McNeilly, Jan 31, 2013, Thiamethoxam. Acute, and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Use of Thiamethoxam on Imported Tea.

D406586, W. Drew, 29 January 2013. Thiamethoxam. Petition to Establish a Permanent Tolerance for Residues of the Insecticide Resulting from Food Use on Imported Tea. Summary of Analytical Chemistry and Residue Data.

D406746. M. Crowley, Dec 4, 2012. Thiamethoxam: Revised Residential Exposure Assessment to Support an Amended Import Tolerance for Coffee.

TXR#: 0056482. Thiamethoxam, Summary of Hazard and Science Policy Council (HASPOC) Meeting of October 11, 2012: Recommendation on the need for a 28-day inhalation study.

D373378, Christopher M. Koper, 20 May 2010. Tier II Drinking Water Exposure Assessment to Establish a Tolerance of Thiamethoxam on Peanut and Alfalfa Seeds.

D363202, Faruque Khan, April 7, 2009. Tier I Drinking Water Exposure Assessment to Establish Thiamethoxam Tolerances for Cranberry and Proposed New Use on Rice Seed Treatment

D382248, Shih-Chi Wang, 7 Dec 2010. Thiamethoxam: Occupational and Residential Exposure/Risk Assessment for Proposed Section 3 Registration for Use in Food/Feed Handling Establishments.

D329466, Michael Doherty, 22 May 2007. Thiamethoxam Human Health Risk Assessment for Proposed New Uses or Revised Uses on Artichoke, Barley, *Brassica* Vegetables, Bushberry, Caneberry, Cotton, Cranberry, Cucurbit Vegetables, Fruiting Vegetables, Hops, Juneberry, Leafy Vegetables, Legume Vegetables, Lingonberry, Mint, Oilseed Crops, Pecan, Pome Fruit, Potato Seed Pieces, Root Vegetables (Except Sugarbeet), Salal, Stone Fruit, Strawberry, Tobacco, Tuberous and Corm Vegetables, and Turf.

Attachments:
Attachment A: Toxicology Profile and Executive Summaries
Attachment B: International Residue Limit Status sheet

Attachment A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food and non-food uses for thiamethoxam are listed below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Test	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity	Yes	Yes
870.1200 Acute Dermal Toxicity	Yes	Yes
870.1300 Acute Inhalation Toxicity	Yes	Yes
870.2400 Primary Eye Irritation	Yes	Yes
870.2500 Primary Dermal Irritation	Yes	Yes
870.2600 Dermal Sensitization	Yes	Yes
870.3100 Oral Subchronic (rodent)	Yes	Yes
870.3150 Oral Subchronic (nonrodent)	Yes	Yes
870.3200 21-Day Dermal	Yes	Yes
870.3250 90-Day Dermal	No	No
870.3465 90-Day Inhalation	No	*
870.3700a Developmental Toxicity (rodent)	Yes	Yes
870.3700b Developmental Toxicity (nonrodent)	Yes	Yes
870.3800 Reproduction	Yes	Yes
870.4100a Chronic Toxicity (rodent)	Yes	Yes
870.4100b Chronic Toxicity (nonrodent)	No	Yes
870.4200a Oncogenicity (rat)	Yes	Yes
870.4200b Oncogenicity (mouse)	Yes	Yes
870.4300 Chronic/Oncogenicity	Yes	Yes
870.5100 Mutagenicity—Gene Mutation - bacterial	Yes	Yes
870.5300 Mutagenicity—Gene Mutation - mammalian	Yes	Yes
870.5385 Mutagenicity—Mammalian Bone Marrow Chromosome Aberration Aberrations	Yes	Yes
870.5550 Mutagenicity—Unscheduled DNA Synthesis	Yes	Yes
870.6200a Acute Neurotoxicity Screening Battery (rat)	Yes	Yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	Yes	Yes
870.6300 Developmental Neurotoxicity	No	Yes
870.7485 General Metabolism	Yes	Yes
870.7600 Dermal Penetration	No	Yes
870.7800 Immunotoxicity	Yes	Yes

*A 28-day repeated dose inhalation study is not required for the currently proposed use patterns. See HASPOC memo (TXR# 0052354) for details.

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity of Technical Thiamethoxam.

GDLN	Study Type	MRID	Results	Tox Category
870.1100	Acute Oral - rat	44703314	LD_{50}: 1563 mg/kg (♂+♀)	III
870.1200	Acute Dermal	44703316	LD_{50} > 2000 mg/kg (♂+♀)	III
870.1300	Acute Inhalation	44703317	LC_{50} > 3.72 mg/L (♂+♀)	IV
870.2400	Primary Eye Irritation	44703318	Minimally irritating	IV
870.2500	Primary Skin Irritation	44703319	Not irritating	IV
870.2600	Dermal Sensitization	44710401	Is not a sensitizer using method of Magnusson and Kligman	N/A

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Thiamethoxam

Type of Study/Guideline	Study Title	MRID	Results
870.3100	28-day Oral Toxicity – Supplementary Range-finding Study rat (diet)	44703322 (1995) ppm=0, 100, 1000, 2500, 10000 (0/0, 8.04/8.69, 81.7/89.3, 199/211, 711/763 mg/kg/day (M/F))	NOAEL = 199/211 mg/kg/day LOAEL = 711/763 mg/kg/day based on decreased body weight (males), increased AST, increased cholesterol, increased liver weight, liver hypertrophy, and fatty change in the adrenal glands.
870.3100	28-day Oral Toxicity – Supplementary Range-finding Study rat (gavage)	44718701 (1994) (0, 100, 300, or 1000 mg/kg/day, M)	NOAEL = 100 mg/kg/day LOAEL = 300 mg/kg/day based on fatty change in the adrenal glands.
870.3100	90-Day Oral Toxicity - rat (diet) Acceptable/ guideline	44718703 (1996) ppm=0, 25, 250, 1250, 2500 & 5000 (0/0, 1.74/1.88, 17.64/19.2, 85/93, 168/182, 329/359 mg/kg/day (M/F))	NOAEL = 17.6 mg/kg/day LOAEL = 85 mg/kg/day based on decreased body weight in males.
870.3100	90-Day Oral Toxicity- mouse (diet) Acceptable/ guideline	44703323 (1996) ppm=0, 10, 100, 1250, 3500 & 7000 (0/0, 1.41/2.01, 14.3/19.2, 176/231, 543/626, 1335/1163 mg/kg/day (M/F))	NOAEL = 176 mg/kg/day LOAEL = 543 mg/kg/day based on respiratory sounds (females), increased liver weight (females), hepatocyte hypertrophy (m/f), liver histopathology (m/f), atrophy of the ovaries (female), and decreased ovary weight (females).

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Thiamethoxam			
Type of Study/Guide line	**Study Title**	**MRID**	**Results**
870.3150	28-day Oral Toxicity – dog (diet) Supplementary Range-finding Study	44703324 (1996) ppm=0, 300, 1000, & 3000 (0/0, 10.0/10/7, 31.6/32.6, 47.7/43.0 mg/kg/day (M/F))	NOAEL = 31.6/32.6 (M/F) mg/kg/day LOAEL = 47.7/43.0 (m/F) mg/kg/day based on body weight loss; leukopenia and increased hematocrit, hemoglobin and erythrocyte count; increased plasma urea and creatinine; reduced thymus weight in males and females, increased thyroid weight in males and reduced brain weight in females; and, histopathological changes in liver, thymus and spleen.
870.3150	13-Week Oral Toxicity- dog (diet) Acceptable/ guideline	44718702 (1998) ppm=0, 50, 250, 1000 & 2500/2000 (after week 2 reduced to 2000) (0/0, 1.58/1.80, 8.23/9.27, 32.0/33.9, 54.8/50.5 mg/kg/day (M/F))	NOAEL = 8.23 (males), 9.27 (females) mg/kg/day LOAEL = 32.0 (males), 33.9 (females) mg/kg/day based on LOAEL= 32 (males) 33.9 (females) mg/kg/day based on slightly prolonged prothrombin times and decreased plasma albumin and A/G ratio (both sexes).
870.3200	28-Day Dermal Toxicity - rat Acceptable/ guideline	44710402 (1996) 0, 20, 60, 250 & 1000 mg/kg/day	NOAEL = 250 (males), 60 (females) mg/kg/day LOAEL = 1000 (males), 250 (females) mg/kg/day based on increased plasma glucose, triglyceride levels, and alkaline phosphatase activity and inflammatory cell infiltration in the liver and necrosis of single hepatocytes in females and hyaline change in renal tubules and a very slight reduction in body weight in males. At higher dose levels in females, chronic tubular lesions in the kidneys and inflammatory cell infiltration in the adrenal cortex were observed.
870.3700a	Developmental Toxicity- rat (gavage) Acceptable/ guideline	44718706 (1998) 44703329 (1995) 44703330 (1995) 0, 5, 30, 200 & 750 mg/kg/day	**Maternal** NOAEL = 30 mg/kg/day LOAEL = 200 mg/kg/day based on decreased body weight, body weight gain, and food consumption. **Developmental** NOAEL = 200 mg/kg/day LOAEL = 750 mg/kg/day based on decreased fetal body weight and an increased incidence of skeletal anomalies.
870.3700b	Developmental Toxicity- rabbit (gavage) Acceptable/ guideline	44718705 (1998) 44703327 (1995) 44703328 (1995) 0, 5, 15, 50 & 150 mg/kg/day	**Maternal** NOAEL = 50 mg/kg/day LOAEL = 150 mg/kg/day based on maternal deaths, hemorrhagic uterine contents and hemorrhagic discharge, decreased body weight and food intake during the dosing period. **Developmental** NOAEL = 50 mg/kg/day LOAEL = 150 mg/kg/day based on decreased fetal body weights, increased incidence of post-implantation loss and a slight increase in the incidence of a few skeletal anomalies/variations.

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Thiamethoxam			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
870.3800	Reproduction (2-Generation)- rat (diet) Acceptable/ guideline	46402904 (2004) ppm=0, 20, 50, 1000 & 2500 (mg/kg/day F_0 M=0, 1.2, 3.0, 61.7,155.6 F_1M=0, 1.5, 3.7, 74.8, 191.5 F_0F=0, 1.7, 4.3, 84.4, 208.8 F_1F=0, 2.1, 5.6, 110.1, 276.6)	**Parental/Systemic** NOAEL = 276.6 mg/kg/day LOAEL = none, no treatment related effects.. **Reproductive** NOAEL = 62 mg/kg/day LOAEL = 156 mg/kg/day based on sperm abnormalities and germ cell loss in F_1 males. **Offspring** NOAEL = 62 mg/kg/day LOAEL = 156 mg/kg/day based on significantly decreased total litter weights of the F1 pups.
870.3800	Reproduction (2-Generation)- rat (diet) Acceptable/ guideline	44718707 (1998) 44703401 (1995) (range-finding) 44703402 (1998) (Addendum) 46402906 (2000) (Pathology Working Group reevaluation)46402902 (2006) (Summary report) ppm=0, 10, 30, 1000 & 2500 (0/0, 0.61/0.80, 1.84/2.37, 61.25/79.20, 158.32/202.06 mg/kg/day (M/F))	**Parental/Systemic** NOAEL = 202 mg/kg/day LOAEL = none, no treatment related effects. **Reproductive** NOAEL = 0.61 mg/kg/day LOAEL = 1.84 mg/kg/day based on increased incidence and severity of tubular atrophy observed in testes of the F_1 generation males. **Offspring** NOAEL = 61.25 mg/kg/day LOAEL = 158.32 mg/kg/day based on reduced body weight during the lactation period in all litters.
870.4100	Chronic (1 year) – dog (diet) Acceptable/ guideline	44718704 (1998) ppm=0, 25, 150, 750 & 1250 (0/0, 0.70/0.79, 4.05/4.49, 21.0/24.6, 42.0/45.1 mg/kg/day (M/F))	NOAEL = 4.05 (males), 4.49 (females) mg/kg/day LOAEL = 21.0 (males), 24.6 (females) mg/kg/day based on increase in creatinine in both sexes, transient decrease in food consumption in females, and occasional increase in urea levels, decrease in ALT, and atrophy of seminiferous tubules in males.
870.4200	Carcinogenicity, 18-Month - mouse (diet) Acceptable/ guideline	44703326 (1998) ppm=0, 5, 20, 500, 1250 & 2500 (0/0, 0.65/0.89, 2.63/3.68, 63.8/87.6, 162/215, 354/479 mg/kg/day (M/F))	NOAEL = 2.63 (males), 3.68 (females) mg/kg/day LOAEL = 63.8 (males), 87.6 (females) mg/kg/day based on hepatocyte hypertrophy, single cell necrosis, inflammatory cell infiltration, pigment deposition, foci of cellular alteration, hyperplasia of Kupffer cells and increased mitotic activity; also, an increase in the incidence of hepatocellular adenoma (both sexes). At higher doses, there was an increase in the incidence of hepatocellular adenocarcinoma (both sexes) and the number of animals with multiple tumors. **evidence of carcinogenicity**

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Thiamethoxam			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
870.4300	Chronic/Carcinogenicity, 2-Year-rat (diet) Acceptable/ guideline	44718708 (1998) ppm (M/F)=0/0, 10/10, 30/30, 500/1000 &1500/3000 (0/0, 0.41/0.48, 1.29/1.56, 21.0/50.3, 63.0/155 mg/kg/day (M/F)	NOAEL = 155 mg/kg/day LOAEL = none, no treatment related effects. **no evidence of carcinogenicity**
870.5100 870.5265	Gene Mutation in *S. typhimurium* and *E. coli* Acceptable/ guideline	44710404 (1995)	No evidence of gene mutation when tested up to 5000 µg/plate. There was no evidence of cytotoxicity.
870.5265	Gene Mutation in *S. typhimurium* Acceptable/ non-guideline (supplementary)	44968301 (1999)	No evidence of gene mutation when tested up to 5000 µg/plate. The S9 fraction was from non-induced mouse liver, Aroclor 1254 induced mouse liver, or thiamethoxam induced mouse liver, following dietary administration of thiamethoxam for 14 days at concentrations up to 2500 ppm.
870.5300	Gene Mutation in Chinese Hamster V79 Cells at HGPRT Locus Acceptable/ guideline	44710405 (1996)	No evidence of gene mutation when tested up to solubility limit.
870.5375	CHO Cell Cytogenetics Acceptable/ guideline	44710403 (1996)	No evidence of chromosomal aberrations when tested up to cytotoxic or solubility limit concentrations.
870.5395	*In vivo* Mouse Bone Marrow Micronucleus Acceptable/ guideline	44710406 (1995)	Negative when tested up to levels of toxicity in whole animals; however no evidence of target cell cytotoxicity.
870.5550	Unscheduled DNA Synthesis in Primary Rat Hepatocytes Acceptable/ guideline	44710407 (1996)	Negative when tested up to precipitating concentrations.

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Thiamethoxam			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
870.6200a	Acute Neurotoxicity Screening Battery-rat (gavage) Acceptable/ guideline	44703320 (1997) 0,100, 500 & 1500 mg/kg	NOAEL = 100 mg/kg/day LOAEL = 500 mg/kg/day based on drooped palpebral closure, decrease in rectal temperature and locomotor activity and increase in forelimb grip strength (males only). At higher dose levels, mortality, abnormal body tone, ptosis, impaired respiration, tremors, longer latency to first step in the open field, crouched-over posture, gait impairment, hypo-arousal, decreased number of rears, uncoordinated landing during the righting reflex test, slight lacrimation (females only) and higher mean average input stimulus value in the auditory startle response test (males only).
870.6200b	Subchronic Neurotoxicity Study-rat (diet) Acceptable/ guideline	44703325 (1998) ppm (M/F)=0/0,10/10, 30/30, 500/1000 & 1500/3000 (0/0,0.7/0.7, 1.9/2.1, 31.8/73.2, 95.4/216.4 mg/kg/day (M/F))	NOAEL = 95.4 (males), 216.4 (females) mg/kg/day, both highest dose tested. LOAEL = not determined. No treatment-related observations at any dose level. May not have been tested at sufficiently high dose levels; however, new study not required because the weight of the evidence from the other toxicity studies indicates no evidence of concern.
870.6300	Developmental Neurotoxicity Study-rat (diet) Acceptable/ non-guideline	46028202 (2003) 46028201 (2003) ppm= 0, 50, 400, 4000 (0/0, 4.3/8.0, 34.5/64.0, 298.7/593.5 mg/kg/day (gestation/lactation))	**Maternal** NOAEL = 298.7 mg/kg/day LOAEL = not determined. No treatment-related observations at any dose level.. **Developmental** NOAEL = 34.5 mg/kg/day LOAEL = 298.7 mg/kg/day based on decreased fetal body weights and weight gain in males and females, reduced brain weight and size in males and females, and significant changes in brain morphometric measurements.

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Thiamethoxam			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
870.7485	Metabolism Study-rat (gavage) Acceptable/ guideline	44703532 (1996) 44703533 (1998) low dose=0.5 mg/kg high dose=100 mg/kg Also: I.V., 0.5 mg/kg	Absorbed rapidly & extensively, widely distributed, followed by very rapid elimination, mostly in urine. Highest tissue concentrations in skeletal muscle: 10-15% of administered dose. Half-life times from tissues ranged from 2-6 hours. Tissue residues after 7 days extremely low. Approximately 84-95% of administered dose excreted in urine & 2.5-6% excreted in feces within 24 hours. < 0.2% detected in expired air. Most excreted as unchanged parent: 70-80% of dose. The major biotransformation reaction is cleavage of oxadiazine ring to corresponding nitroguanidine compound. Minor pathways: (1) cleavage of nitroguanidine group yielding guanidine derivative, (2) hydrolysis of guanidine group to corresponding urea, (3) demethylation of guanidine group, and (4) substitution of the chlorine of the thiazole ring by glutathione. Cleavage between thiazole- and oxadiazine ring occurs to a small extent. Glutathione derivatives prone to further degradation of the glutathione moiety resulting in various sulfur-containing metabolites (e.g. mercapturates, sulfides, and sulfoxides). Both the thiazole and oxadiazine moiety susceptible to oxidative attack. Small but measurable amounts exhaled, most probably as CO_2. Metabolites eliminated very rapidly. Enterohepatic circulation negligible.
870.7485	Metabolism Study – mice (gavage) Supplementary/ non-guideline	44710408 (1998) 46161502 (2003) 46161505 (2002) 46161512 (2000) (44710408) males only: 118 mg/kg/day, 14 days	Approximately 72% of administered dose excreted in the urine; 19% excreted in feces. Small but measurable amount detected in expired air (approximately 0.2% of dose). Predominant metabolites: unchanged parent (33-41% of administered dose); 2 other metabolites: 8-12% and 9-18% of administered dose. These are the same structures that were most commonly observed in rat excreta; however the proportions are quite different in mouse excreta. One additional significant metabolite (mouse R6) was isolated from feces samples. Between 30-60% of the administered dose was excreted as metabolites.
870.7600	Dermal Absorption – rats; *In vivo*; WG Formulation 25% a.i. unacceptable/ not upgradable	44703403 (1998) Exposure duration	Estimates of dermal absorption were based on the sum of radioactivity in skin test site, urine, feces, blood, and carcass. After 24 hour exposure, dermal absorption estimate is 27%, which is the maximum observed for all dose groups.

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Thiamethoxam			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
870.7600	Dermal Absorption – rats; 2 *in vivo* studies using 21.1 or 48.6% a.i. Formulations; Acceptable/ Guideline	4520001 (2000) 3.64, 36.4 µg/cm^3 Exposure duration?	Estimates of dermal absorption were based on the sum of radioactivity in skin test site, urine, feces, blood, and carcass. After 10 hour exposure, dermal absorption estimate is 5%, which is the maximum observed for all dose groups.
870.7800	Immunotoxicity - mice Acceptable/ Guideline	48547101 (2011) ppm=0, 100, 1250, 5000 (0/0,37.7/36.7, 461.6/433.9, 2026/2024 mg/kg/day (M/F))	**Systemic:** LOAEL = 2025 mg/kg/day based on decreased body weights and body weight gains in females. NOAEL = 1250 ppm (461.6 mg/kg/day) **Immunotoxicity**: LOAEL = Not Determined NOAEL = 5000 ppm (2025 mg/kg/day)
Non-guideline	Hepatic Cell Proliferation - mouse (diet) Acceptable/ non-guideline	44703406 (1998) ppm=100, 500 & 2500 (16/20, 72/87, 386/483 mg/kg/day(M/F))	NOAEL = 16 (males), 20 (females) mg/kg/day LOAEL = 72 (males), 87 (females) mg/kg/day based on proliferative activity of hepatocytes. At higher dose levels, increases in absolute and relative liver wts, speckled liver, hepatocellular glycogenesis/fatty change, hepatocellular necrosis, apoptosis and pigmentation were observed.
Non-guideline	Replicative DNA Synthesis in 28-Day Study-rat, male only (diet) Acceptable/ non-guideline	44703405 (1995) ppm=0, 100, 1000, 2500 & 10000 (0, 8, 82, 199, 711 mg/kg/day)	NOAEL = 711 mg/kg/day (highest dose tested) LOAEL = not established. Immunohistochemical staining of liver sections from control and high-dose animals for proliferating cell nuclear antigen gave no indication for a treatment-related increase in the fraction of DNA synthesizing hepatocytes in S-phase. CGA 293343 did not stimulate hepatocyte cell proliferation in male rats.
Non-guideline	Special study to assess liver biochemistry-mouse Acceptable/ non-guideline	44703407 (1998) doses	NOAEL = 17 (males), 20 (females) mg/kg/day LOAEL = 74 (males), 92 (females) mg/kg/day based on marginal to slight increases in absolute and relative liver weights, a slight increase in the microsomal protein content of the livers, moderate increases in the cytochrome P450 content, slight to moderate increases in the activity of several microsomal enzymes, slight to moderate induction of cytosolic glutathione S-transferase activity. Treatment did not affect peroxisomal fatty acid ß-oxidation.

Table A.2.2. Subchronic, Chronic and Other Toxicity Profile for Thiamethoxam			
Type of Study/Guideline	**Study Title**	**MRID**	**Results**
Non-guideline	Receptor binding study with thiamethoxam, imidacloprid, and nicotine: Interaction with mammalian nicotinic acetylcholine receptors Acceptable/ non-guideline	46402911 (2004) doses	Thiamethoxam had low affinity and was essentially inactive in the binding assay

A.3 Executive Summaries

Dermal Penetration Studies

Two *in vivo* rat dermal absorption studies with formulations of thiamethoxam were available. In the first study (MRID 44703403), thiamethoxam technical was formulated as a water dispersible granular containing 25% thiamethoxam technical and applied to rats at doses of 2.5, 25.3, and 242 µg/cm^2 for 6 hours followed by washing with exposure measured out to 48 hours. In the second study (MRID 45200001), thiamethoxam was applied as Helix 289 FS (21.1% technical) and Adage 5FS (48.6% technical) formulations to rats at doses of 3.64 (Helix only) and 36.4 µg/cm^2 (Helix and Adage) for 10 hours followed by washing with exposure measured out to 336 hours.

In both studies, 20-28% of the test material was still left at the skin site. In the first study, it did not appear that the remaining test material was absorbed over time based on the following: 1) the systemic absorption was similar following sacrifice at 6 and 48 hours post exposure and 2) following 6 hours of exposure there was a relatively large amount of radioactivity in the carcass that decreased with time at all doses, suggesting that the increased levels of radioactivity in the urine at later times points was not coming from the skin but from slow elimination of chemical that was already absorbed. The radioactivity at the skin site also did not appear to be available for further absorption over time in the second study. Similar levels of radioactivity were detected at the skin site across all time points. While there was an increase in the levels of radioactivity in the urine, this was attributed to the animals gaining access to the dose site during the last 7 days of the experiments. Taken together, the two studies support that the radioactivity at the skin site was not available for absorption.

The highest percentage of dermal absorption in the first study was measured as 2.87% at a dose of 25.3 µg/cm^2 48 hours post exposure, although this value was considered to be a potential underestimate of dermal absorption since the exposure was only for 6 hours and residual urine was not collected from the bladder. The highest level of dermal absorption in the second study was 4.22% with the low dose Helix formulation at 336 hours post dose. This is a conservative

estimate of dermal absorption since it likely includes some level of oral exposure from the animals gaining access to the dosing site.

The physical chemistry properties of thiamethoxam also support a low dermal absorption value (i.e., the low Log kow of -0.13). Using the National Institute for Occupational Health and Safety (NIOSH) finite dose skin permeation calculator (http://www.cdc.gov/niosh/topics/skin/finiteSkinPermCalc.html) and the physical chemical properties of thiamethoxam (see appendix for a full list), no dermal absorption (0%) was predicted over an 8 hour period with a dermal load of 3 µg/cm^2. The Finite Dose Skin Permeation Calculator was developed through support of a Center of Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH) grant, and provides an estimation of fluxes, skin concentrations, and amounts absorbed from any size dose applied to partially or fully hydrated skin, using the physicochemical properties of the test compound and defined exposure parameters (Kasting, G.B. 2006; Wang, T.F. 2007; Kasting, G.B. 2008; Miller, M.A. 2010). Currently, OPP does not rely on (Q)SAR modeling alone to derive a Dermal Absorption Factor (DAF) for risk assessment. However, estimates from the Finite Dose Skin Permeation Calculator may be used with read across data to support a weight of the evidence evaluation.

Attachment B: Physical/Chemical Characteristics

Table B. Physicochemical Properties of Thiamethoxam.			
Parameter	Value		Reference
Melting point/range	139.1°C		PMRA Regulatory Note (REG2001-03) on Thiamethoxam, 2/9/01
pH	4.7 (1% solution in water)		
Density	1.57 g/cm^3		
Water solubility	4.1 g/L (25°C)		
Solvent solubility	Solvent acetone dichloromethane ethyl acetate hexane methanol octanol toluene	Solubility (g/L) 48 110 7.0 <1 mg/L 13 0.62 0.68	
Vapor pressure	2.7 x 10^{-9} Pa (20°C) 6.6 x 10^{-9} Pa (25°C)		
Dissociation constant, pK_a	No dissociation within the pH range 2–12		
Octanol/water partition coefficient, Log(K_{OW})	0.13 (25°C)		
UV/visible absorption spectrum	Not available		

Thiamethoxam is a solid under ambient conditions and has low volatility. The compound has relatively low solubility in nonpolar organic solvents, and its octanol/water partition coefficient suggests that accumulation of thiamethoxam in fatty tissues is unlikely to occur.

Attachment C: International Residue Limits

Thiamethoxam (PC Code 060109)				
US Tolerance and International Maximum Residue Limits for Banana.				
Residue Definitions				
US		**Canada**	**Mexico[1]**	**Codex**
40CFR §180.565 **Crops/Livestock:** Thiamethoxam (3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl- N-nitro-4H-1,3,5-oxadiazin-4-imine) and its metabolite, CGA-322704 (N-(2-chloro-thiazol-5-ylmethyl)-N'-methyl- N'-nitro-guanidine), calculated as the stoichiometric equivalent of thiamethoxam.		3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl- N-nitro-4H-1,3,5-oxadiazin-4-imine) and its metabolite, N-(2-chloro-thiazol-5-ylmethyl)-N'-methyl-N'-nitro-guanidine		Thiamethoxam.
Commodity[2]	**Tolerance (ppm)[3]**	**Maximum Residue Limit (mg/kg)**		
	US	**Canada**	**Mexico[1]**	**Codex**
Banana	0.03			0.02
Completed: W.T. Drew; 13 January 2016.				

1. Mexico adopts US tolerances, and/or Codex MRLs, for its export purposes.
2. Includes only commodities of interest for this action.
3. Tolerance values are those recommended by HED, not those proposed by the petitioner.